BRAND-Name Savings May Be Waiting for You*

Use these tips along with your GEODON Savings Card when picking up your brand-name prescription.

Begin

at your doctor’s office.

Remind

your doctor to indicate “Dispense As Written” (“DAW”) or “No Substitutions,” as per your state’s requirement if your doctor has decided to prescribe brand-name GEODON.

Ask

for brand-name GEODON at the pharmacy, and tell your pharmacist your GEODON Savings Card does not work with the generic.

Notify

the pharmacist right away if you did not receive brand-name GEODON or your savings at pick-up.

Don’t

forget your GEODON Savings Card each time you visit the pharmacy.

*Terms and conditions apply. See below.

If you didn’t get the brand-name savings that come with your GEODON Savings Card and you meet all eligibility requirements, check to make sure:

• You received brand-name GEODON in your prescription bag. Your card works only with brand-name GEODON
• Your GEODON Savings Card details were entered correctly
• Your pharmacist called 1-800-725-9655 for help processing the card for this brand

GEODON is available in 20-mg, 40-mg, 60-mg, and 80-mg capsules as well as in intramuscular injection in 20-mg/mL single-use vials.

*Eligibility required. Terms and conditions apply. Full terms and conditions can be found at GEODON.com/about-copay#terms. Card accepted only at participating pharmacies. Card is not health insurance. No membership fees. Maximum benefit of $3,000 per year. The Card is not valid for prescriptions that are eligible to be reimbursed in whole or in part, by Medicaid, Medicare, or other federal or state healthcare programs. The Card is not valid for prescriptions that are eligible to be reimbursed in whole by private insurance plans or other health or pharmacy benefit programs. For more information, call 1-800-725-9655, visit www.GEODON.com, or write: Attn: GEODON Savings Card: 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (5.1).
- GEODON is not approved for elderly patients with dementia-related psychosis (5.1).

RECENT MAJOR CHANGES

Boxed Warning
- 11/2018
Dosage and Administration (2.4)
- Removed 11/2018
Warnings and Precautions (5.1, 5.2)
- 11/2018

INDICATIONS AND USAGE

GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the capacity of GEODON to prolong the QT interval and may consider the use of other drugs first (5.3).

GEODON is indicated as an oral formulation for:
- Treatment of schizophrenia (1).
- Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder (1).
- Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate (1).

GEODON is also indicated as an intramuscular injection for:
- Acute treatment of agitation in schizophrenic patients (1).

DOSE AND ADMINISTRATION

Give oral doses with food.

- Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be increased up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days. Safety and efficacy has been demonstrated in doses up to 100 mg twice daily. The lowest effective dose should be used (2.1).
- Acute treatment of manic/mixed episodes of bipolar I disorder: Initiate at 40 mg twice daily. Increase to 60 to 80 mg or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40-80 mg twice daily (2.2).
- Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-90 mg twice daily (2.2).
- Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10 mg-20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours (2.3).

CONTRAINDICATIONS

- Do not use in patients with a known history of QT prolongation (4.1).
- Do not use in patients with recent acute myocardial infarction (4.1).
- Do not use in patients with uncompensated heart failure (4.1).
- Do not use in combination with other drugs that have demonstrated QT prolongation (4.1).
- Do not use in patients with known hypersensitivity to ziprasidone (4.2).

WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.2).
- QT Interval Prolongation: GEODON use should be avoided in patients with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval, or in combination with other drugs that have demonstrated QT prolongation (5.3).
- Neuroleptic Malignant Syndrome (NMS): Potentially fatal symptom complex has been reported with antipsychotics. Manage with immediate discontinuation of drug and close monitoring (5.4).
- Severe Cutaneous Adverse Reactions: Such Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome has been associated with ziprasidone exposure. DRESS and other Severe Cutaneous Adverse Reactions (SCAR) are sometimes fatal. Discontinue GEODON if DRESS or SCAR are suspected (5.5).
- Tardive Dyskinesia: May develop acutely or chronically (5.6).
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.7).
- Hyperglycemia and Diabetes Mellitus (DM): Monitor all patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients with DM risk factors should undergo glucose testing before and during treatment (5.7).
- Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics (5.7).
- Weight Gain: Weight gain has been reported. Monitor weight gain (5.7).
- Rash: Discontinue in patients who develop a rash without an identified cause (5.8).
- Orthostatic Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease (5.9).
- Leukopenia, Neutropenia, and Agranulocytosis has been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue GEODON at the first sign of a decline in WBC in the absence of other causative factors (5.11).
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold (5.12).
- Potential for Cognitive and Motor Impairment: Patients should use caution when operating machinery (5.13).
- Suicide: Closely supervise high-risk patients (5.18).

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and at least twice the incidence for placebo) were:
- Schizophrenia: Somnolence, respiratory tract infection (6.1).
- manic and mixed episodes associated with bipolar disorder: Somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthma, vomiting (6.1).
- Intramuscular administration (≥5% and at least twice the most intramuscular ziprasidone group): Headache, nausea, somnolence (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ziprasidone should not be used in combination with other drugs that have demonstrated QT prolongation (4.1, 7.3).
- The absorption of ziprasidone is increased up to two-fold in the presence of food (7.10).
- The full prescribing information contains additional drug interactions (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk (8.1).
- Nursing Mothers: Breastfeeding is not recommended (8.3).
- Pediatric Use: Antipsychotic use in pediatric patients has not been established (8.4).
- Renal Impairment: Intramuscular ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 HOW SUPPLIED/STORAGE AND HANDLING
16 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
1 INDICATIONS AND USAGE
GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients. When deciding among the alternative treatments available for the condition needing treatment, the prescriber should consider the finding of ziprasidone’s greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs [see Warnings and Precautions (5.3)]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de points-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de points or increase the rate of sudden death is not yet known [see Warnings and Precautions (5.3)]

Schizophrenia
• GEODON is indicated for the treatment of schizophrenia in adults [see Clinical Studies (14.1)].

Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)
• GEODON is indicated as monotherapy for the acute treatment of adults with manic or mixed episodes associated with bipolar I disorder [see Clinical Studies (14.2)].
• GEODON is indicated as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder in adults [see Clinical Studies (14.2)].

Acute Treatment of Agitation in Schizophrenia
• GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic adult patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation [see Clinical Studies (14.1)]. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia
Dose Selection
GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily. However, results were not consistent in the range of 80 mg to 160 mg twice daily. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [see Clinical Studies (14.1)].

Maintenance Treatment
While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been treated with ziprasidone for more than three consecutive days has not been studied.

Acute Treatment of Manic or Mixed Episodes
Dose Selection
The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

The intramuscular dose should be administered at not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in bipolar disorder was demonstrated in a dose range of 20 mg to 80 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily. However, results were not consistent in the range of 80 mg to 160 mg twice daily. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [see Clinical Studies (14.1)]. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Intramuscular Preparation for Administration
GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solids other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS
GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with “PZER and ZDX [dosage strength]” or “PZER” and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules
Capsule Strength (mg) Imprint OR GEODON Capsules
Capsule Strength (mg) Imprint
20 ZDX 20 20 396
40 ZDX 40 40 397
60 ZDX 60 60 398
80 ZDX 80 80 399

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) [see Dosage and Administration (2.3)]. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized to 294 mg of sulfobutyl ether β-cyclodextrin sodium (SBECD).

4 CONTRAINDICATIONS

4.1 QT Prolongation
Because of ziprasidone’s dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated:
• in patients with a known history of QT prolongation (including congenital long QT syndrome)
• in patients with recent acute myocardial infarction
• in patients with uncompensated heart failure
Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not have been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:
• dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mexitidine, mibefradil, verapamil, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, metapline, pentamidine, arsine trioxide, levomepromazine acetate, dolasetron mesylate, proscyllin or talcromil.
• other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning [see Warnings and Precautions (5.3)].

4.2 Hypersensitivity
Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON is not approved for the treatment of dementia-related psychosis. [see Boxed Warning, Warnings and Precautions (5.1)].

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. GEODON is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.2)].

5.3 QT Prolongation and Risk of Sudden Death
Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval [see Contraindications (4.1) and Drug Interactions (7.4)]. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias [see Contraindications (4)].

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

Additional studies directly comparing the QT/QTc prolonging effect of intramuscular ziprasidone with several other drugs effective in the treatment of schizophrenia were conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.
In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection.

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case of torsade de pointes was reported, and both cases were reported in patients who received placebo. In the ziprasidone-treated patients, the QTc intervals exceeding the potentially clinically relevant threshold of 500 msec were reported in patients who received placebo. In the ziprasidone-treated patients, the QTc intervals exceeding the potentially clinically relevant threshold of 500 msec were reported in patients who received placebo.

Persistently prolonged QTc intervals may also increase the risk of further prolongation and torsade de pointes, especially in patients with congenital QT prolongation. In the ziprasidone-treated patients, neither case of torsade de pointes was reported, and both cases were reported in patients who received placebo. In the ziprasidone-treated patients, the QTc intervals exceeding the potentially clinically relevant threshold of 500 msec were reported in patients who received placebo. In the ziprasidone-treated patients, the QTc intervals exceeding the potentially clinically relevant threshold of 500 msec were reported in patients who received placebo.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and sudden unexpected death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in prematurity care and treatment, it is prudent to periodically monitor QTc at baseline and throughout treatment. The QTc interval should be measured at baseline and periodically throughout treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential symptomatic suppression has upon the long-term course of the syndrome is unknown. In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. It is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in prematurity care and treatment, it is prudent to periodically monitor QTc at baseline and throughout treatment. The QTc interval should be measured at baseline and periodically throughout treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment.

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In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random glucose for ziprasidone 20-40 mg BID was -3.4 mg/dL (N=122); for ziprasidone 60-80 mg BID was +1.3 mg/dL (N=10); and for placebo was +0.3 mg/dL (N=71).

**Table 3: Glucose**

<table>
<thead>
<tr>
<th>Mean Fasting Glucose Change from Baseline mg/dL (N)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose: 20-40 mg BID</td>
<td>+0.1 (N=206)</td>
<td>+1.6 (N=166)</td>
</tr>
</tbody>
</table>

*Fasting

**Table 4: Glucose**

<table>
<thead>
<tr>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>Ziprasidone</td>
<td>272</td>
<td>5 (1.8%)</td>
</tr>
<tr>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>Placebo</td>
<td>210</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Borderline to High (≥100 mg/dL to &lt;126 mg/dL)</td>
<td>Ziprasidone</td>
<td>79</td>
<td>12 (15.2%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>71</td>
<td>7</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

*Fasting

**Table 5: Lipid**

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Normal to High (&lt;150 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>68</td>
<td>232 (34.1%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>260</td>
<td>53</td>
<td>20.4%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>429</td>
<td>63 (14.7%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>152</td>
<td>12</td>
<td>7.9%</td>
</tr>
<tr>
<td></td>
<td>Increase by ≥40 mg/dL</td>
<td>Ziprasidone</td>
<td>682</td>
<td>76 (11.1%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>261</td>
<td>26</td>
<td>10.0%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥200 mg/dL to ≥240 mg/dL)</td>
<td>Ziprasidone</td>
<td>380</td>
<td>15 (3.9%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>145</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Table 6: Lipid**

**Table 7: Lipid**

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Normal to High (&lt;100 mg/dL to ≥160 mg/dL)</td>
<td>Ziprasidone</td>
<td>247</td>
<td>69 (27.8%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>195</td>
<td>22</td>
<td>11.7%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥100 mg/dL to ≥160 mg/dL)</td>
<td>Ziprasidone</td>
<td>228</td>
<td>28 (12.6%)</td>
</tr>
</tbody>
</table>

*Fasting

**Table 8: Lipid**

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Increase by ≥50 mg/dL</td>
<td>Ziprasidone</td>
<td>371</td>
<td>66 (17.8%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>286</td>
<td>62</td>
<td>21.7%</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>Normal to High (&lt;100 mg/dL to ≥240 mg/dL)</td>
<td>Ziprasidone</td>
<td>225</td>
<td>15 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>179</td>
<td>13</td>
<td>7.3%</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Borderline to High (≥100 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>58</td>
<td>16 (27.6%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>14</td>
<td>29.8%</td>
</tr>
</tbody>
</table>

*Fasting

**Table 9: Weight**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>371</td>
<td>66 (17.8%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>286</td>
<td>62 (21.7%)</td>
</tr>
</tbody>
</table>

**Table 10: Summary of Weight Change**

**Table 11: Summary of Weight Change**

**Table 12: Summary of Weight Change**

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline weight for ziprasidone 20-40 mg BID was -2.3 kg (N=124); for ziprasidone 60-80 mg BID was +2.5 kg (N=10); and for placebo was -2.9 kg (N=72). In the same long-term studies, the proportion of subjects with a weight gain criterion of ≥7% increase in weight from baseline for ziprasidone 20-40 mg BID was 5.6% (N=124); for ziprasidone 60-80 mg BID was 0.0% (N=10), and for placebo was 5.6% (N=72). In a long-term (at least 1 year), placebo-controlled, fixed-dose study in schizophrenia, the mean change from baseline weight for ziprasidone 20 mg BID was -2.6 kg (N=72); for ziprasidone 40 mg BID was -3.3 kg (N=69); for ziprasidone 80 mg BID was -2.8 kg (N=70) and for placebo was -3.8 kg (N=70). In the same long-term fixed-dose schizophrenia study, the proportion of subjects with a weight change criterion of ≥3 kg to ≥7 kg and ≥7 kg was 11.9% (N=124) respectively for ziprasidone 20 mg BID (N=72); for ziprasidone 40 mg BID (N=69); for ziprasidone 80 mg BID (N=70) and for placebo was 2.7% (N=70). **Table 12: Summary of Weight Change**: In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline weight for ziprasidone 20-40 mg BID was -2.3 kg (N=124); for ziprasidone 60-80 mg BID was +2.5 kg (N=10); and for placebo was -2.9 kg (N=72). In the same long-term studies, the proportion of subjects with ≥7% increase in weight from baseline for ziprasidone 20-40 mg BID was 5.6% (N=124); for ziprasidone 60-80 mg BID was 0.0% (N=10), and for placebo was 5.6% (N=72). In a long-term (at least 1 year), placebo-controlled, fixed-dose study in schizophrenia, the mean change from baseline weight for ziprasidone 20 mg BID was -2.6 kg (N=72); for ziprasidone 40 mg BID was -3.3 kg (N=69); for ziprasidone 80 mg BID was -2.8 kg (N=70) and for placebo was -3.8 kg (N=70). In the same long-term fixed-dose schizophrenia study, the proportion of patients who entered the program with a “high” BMI was 4.0% (N=124) respectively for ziprasidone 20 mg BID (N=72); for ziprasidone 40 mg BID (N=69); for ziprasidone 80 mg BID (N=70) and for placebo was 2.7% (N=70).
5.17 Body Temperature Regulation
Although not reported with ziprasidone in premarking trials, disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.18 Suicide
The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

5.19 Patients with Concomitant Illnesses
Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited (see Use in Specific Populations (8.6), (8.7)).

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarking clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients. [see Warnings and Precautions (5.3), (5.9)].

5.20 Laboratory Tests
Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec. [see Warnings and Precautions (5.3)].

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. Experience in these patients include: (1) 4351 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. An additional 127 patients with bipolar disorder participated in a long-term maintenance treatment study representing approximately 74.7 patient-years of exposure to ziprasidone. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

Clinical trials for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse reactions during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone
The following findings are based on the short-term placebo-controlled premarking trials for schizophrenia (a pool of 2-week, and 2-week fixed-dose trials) and bipolar mania (a pool of 2-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials
The following adverse reactions were the most commonly observed adverse reactions associated with the use of ziprasidone (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (ziprasidone incidence at least twice that for placebo):

Schizophrenia trials (see Table 11)

- Somnolence
- Respiratory Tract Infection

Bipolar trials (see Table 12)

- Somnolence
- Extrapyramidal Symptoms which includes the following adverse reaction terms: extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, paroxysmal and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
- Dizziness which includes the adverse reaction terms dizziness and lightheadedness.
- Akathisia
-Abnormal Vision
- Asthenia
-Vomiting

SCHIZOPHRENIA

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone
Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients [see Warnings and
Dystonia
the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled reaction terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, ADS

Table 11: Treatment-Emergent Adverse Reaction Incidence In Short-Term Oral Placebo-Controlled Trials – Schizophrenia

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ziprasidone (N=702)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>4</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>14</td>
</tr>
<tr>
<td>Somnolence</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness**</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>8</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
</tr>
<tr>
<td>Fungal Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>3</td>
</tr>
</tbody>
</table>

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paroxysm, and twitching. None of these adverse reactions occurred individually at an incidence greater than 5% in schizophrenia trials.

** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Dose Dependency of Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials
An analysis for dose responsiveness in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypotension, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS) - The incidence of reported EPS (which included the adverse reaction terms extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, paroxysm, and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Dystonia - Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Vital Sign Changes - Ziprasidone is associated with orthostatic hypotension [see Warnings and Precautions (5.9)].

ECG Changes - Ziprasidone is associated with an increase in the QTc interval [see Warnings and Precautions (5.3)]. In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to 0.2 beats per minute decrease among placebo patients. Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported reactions are included except those already listed in Table 11 or elsewhere in labeling, those reaction terms that were so general as to be uninformative, reactions reported only once and that did not have a substantial probability of being acutely life-threatening, reactions that are part of the illness being treated or are otherwise common as background reactions, and reactions considered unlikely to be drug-related. It is important to emphasize that, although the reactions reported occurred during treatment with ziprasidone, they were not necessarily caused by it. Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions:

- Frequent - adverse reactions occurring in at least 1/100 patients (≥1.0% of patients) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing);
- Infrequent - adverse reactions occurring in 1/100 to 1/1000 patients (0.1-1.0% of patients);
- Rare - adverse reactions occurring in fewer than 1/1000 patients (<0.1% of patients).

Body as a Whole
Frequent - abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

Cardiovascular System
Frequent - tachycardia, hypertension, postural hypotension
Infrequent - bradycardia, angina pectoris, atrial fibrillation
Rare - first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomyopathy, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis

Digestive System
Frequent - anorexia, vomiting
Infrequent - rectal hemorrhage, dysphagia, tongue edema
Rare - gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatectomy, leukoplakia of mouth, fatty liver deposit, melena

Endocrine
Rare - hypothyroidism, hyperthyroidism, thyroiditis

Hemic and Lymphatic System
Infrequent - anemia, eosinophilia, leukopenia, lymphopenaphy
Rare - thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocytopenia

Metabolic and Nutritional Disorders
Infrequent - thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesterolemia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia
Rare - BUN increased, creatinine increased, hyperlipemia, hypercholesterolemia, hyperkalemia, hypoglycemia, hypernatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperuricemia, hyperuricosuria, hypercalcemia, hypoglycemic reaction, hypoglycemenemia, ketosis, respiratory alkalosis

Musculoskeletal System
Frequent - myalgia
Infrequent - tenosynovitis
Rare - myopathy

Nervous System
Frequent - agitation, extrapyramidal syndrome, tremor, dystonia, hypotonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypothermia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy
Infrequent - paralyis
Rare - myoclonus, dystagmus, torticollis, circumoral paresthesia, opisthotonus, reflexes increased, trismus

Respiratory System
Frequent - dyspnea
Infrequent - pneumonia, epistaxis
Rare - hemoptysis, laryngismus

Skin and Appendages
Infrequent - maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash

Special Senses
Frequent - fungal dermatitis
Infrequent - conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia
Rare - eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis

Urogenital System
Infrequent - impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention metorrhagia, male sexual dysfunction, anorgasms, glycosuria
Rare - gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage

BIPOLAR DISORDER
Acute Treatment of Manic or Mixed Episodes
Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials
Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (9/256) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse reactions.
**Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials**

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Ziprasidone 2 mg (N=279)</th>
<th>Placebo (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Increased Salivation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tongue Edema</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness**</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Speech Disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal Dermatitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.

**Digestive**  
Nausea 10 7
Diarrhea 5 4
Dry Mouth 5 4
Vomitting 5 2
Increased Salivation 4 0
Tongue Edema 3 1
Dysphagia 2 0

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Ziprasidone 2 mg (N=279)</th>
<th>Placebo (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Explanations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of this demographic factor.

**INTRAMUSCULAR ZIPRASIDONE**  
Adverse Reactions Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients. Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients treated with ziprasidone.

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Ziprasidone 2 mg (N=92)</th>
<th>Ziprasidone 10 mg (N=63)</th>
<th>Ziprasidone 20 mg (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GEODON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following: Cardiac Disorders: Tachycardia, torda de pontes (in the presence of multiple confounding factors), (see Warnings and Precautions (5.3)); Digestive System Disorders: Swollen Tongue; Reproductive System and Breast Disorders: Galactorrhea, priapism; Nervous System Disorders: Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; Psychiatric Disorders: Insomnia, mania/hypomania; Skin and Subcutaneous Tissue Disorders: Allergic reaction (such as allergic dermatitis, angioedema, pruritus, urticaria), rash, Drug Reaction with Eosinophilia and Systemic Symptoms (DRRESS); Urogenital System Disorders: Enuresis, urinary incontinence; Vascular Disorders: Postural hypotension, syncope.

7 DRUG INTERACTIONS

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated.

7.1 Metabolic Pathway

Approximately two-thirds of ziprasidone is metabolized via a combination of chemical reduction by glutathione and enzymatic reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase. Less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation.

7.2 In Vitro Studies

An in vitro enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes.
7.3 Pharmacodynamic Interactions
Ziprasidone should not be used with any drug that prolongs the QT interval [see Contraindications (4.1)]. Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

7.4 Pharmacokinetic Interactions
Carbamazepine
Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketocazone
Ketocazone, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine
Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid
The co-administration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

7.5 Lithium
Ziprasidone at a dose of 40 mg twice daily administered concomitantly with lithium at a dose of 450 mg twice daily for 7 days did not affect the steady-state level or renal clearance of lithium. Ziprasidone doses adjunctively to lithium in a maintenance trial of bipolar patients did not affect mean therapeutic lithium levels.

7.6 Oral Contraceptives
In vivo studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progestosterone components. Ziprasidone at a dose of 20 mg twice daily did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

7.7 Dextromethorphan
Consistent with in vitro results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrophan ratio.

7.8 Valproate
A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. Ziprasidone doses adjunctively to valproate in a maintenance trial of bipolar patients did not affect mean therapeutic valproate levels.

7.9 Other Concomitant Drug Therapy
Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

10.3 Individual Laboratory Function

There is little potential for drug interactions with ziprasidone due to displacement [see Clinical Pharmacology (12.3)].

There was an increase in the number of pups born dead and a decrease in postnatal survival throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m² basis) during organogenesis or doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m² basis) or greater. A no-effect level was not and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m² basis) or greater. A no-effect level was not been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery
The effect of ziprasidone on labor and delivery in humans is unknown.

8.3 Nursing Mothers
It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed.

8.4 Pediatric Use
The safety and effectiveness of ziprasidone in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

8.6 Renal Impairment
Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based on the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cycloextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis increased an increase in AUC, of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

8.8 Age and Gender Effects
In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (≥65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

8.9 Smoking
Based on in vitro studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these in vitro results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence
Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience
In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage with ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3,240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Adverse reactions reported with ziprasidone overdose included extrapyramidal symptoms, somnolence, tremor, and anxiety. [see Adverse Reactions (6.2)]

10.2 Management of Overdose
In case of accidental overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established, and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dysrhythmic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.
to a much lesser extent. Based on in vivo abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

### Intramuscular Pharmacokinetics

#### Systemic Bioavailability

The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_1/2$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

#### Metabolism and Elimination

Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**

Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the MRHD of 200 mg/day on a mg/m² basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m² basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m² basis). Ziprasidone had no effect on serum prolactin in rats in a 90-day study at doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.14)].

**Mutagenesis**

Ziprasidone was tested in the Ames bacterial mutation assay, the in vitro mammalian cell gene mutation assay, the in vitro chromosomal aberration assay in human lymphocytes, and the in vivo chromosomal aberration assay in mouse bone marrow. There was a reproducible increase in the frequency of sister chromatid exchange in the mouse bone marrow in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes.

**Impairment of Fertility**

Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m² basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m² basis) there were no treatment-related findings observed in the tests.

### 14 CLINICAL STUDIES

#### 14.1 Schizophrenia

The results of the oral ziprasidone trials in the treatment of schizophrenia were evaluated in 5 placebo-controlled trials, 4 short-term (4- and 6-week) trials and one maintenance trial. All trials included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment for the oral ziprasidone studies, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the efficacy of new drugs in schizophrenia. The Brief Psychiatric Rating Scale (BPRS) consists of 18 items representing positive symptoms (hallucinatory behavior, suspiciousness, and unusual thought content) and is considered a useful subset for assessing actively psychotic schizophrenic patients. A second widely used measure, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessment of Negative Symptoms (SANS) is used for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:

- **In a 4-week, placebo-controlled trial (n=139)** comparing 2 fixed doses of ziprasidone (20 and 60 mg twice daily) with placebo, only the 60 mg dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.
- **In a 6-week, placebo-controlled trial (n=302)** comparing 2 fixed doses of ziprasidone (40 and 80 mg twice daily), both groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg twice daily had a numerically greater effect than 40 mg twice daily, the difference was not statistically significant.
- **In a 12-week, placebo-controlled trial (n=419)** comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg twice daily) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg twice daily dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg twice daily to 100 mg twice daily dose range.
In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg twice daily), none of the dose groups was statistically superior to placebo on any outcome of interest.

A study was conducted in stable chronic or subchronic (CGI-S 5-6 at baseline) schizophrenic inpatients (n=294) who had been hospitalized for not less than two months. After a 3-day single-blind placebo run-in, subjects were randomized to one of 3 fixed doses of ziprasidone (20 mg, 40 mg, or 80 mg twice daily) or placebo and observed for a period of 30 days to determine relapse. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or score ≤6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in time to relapse, with no significant difference between the different dose groups. The results of this study demonstrated that ziprasidone was effective in the prevention of relapse in a predominantly chronic inpatient population.

14.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Acute Manic and Mixed Episodes Associated with Bipolar I Disorder

The efficacy of ziprasidone was established in 2 placebo-controlled, double-blind, 3-week monotherapy studies in patients meeting DSM-IV criteria for bipolar I disorder, manic or mixed episode with or without psychotic features. Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in adult bipolar I disorder, manic/mixed episode follow: in a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg. In a second 3-week placebo-controlled trial (n=295), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Maintenance Therapy

The efficacy of ziprasidone as adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder was established in a placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder. The trial included GT prolongation; risk for significant episode was manic or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilized on ziprasidone plus lithium or valproic acid for at least 8 weeks in order to be randomized. In the double-blind randomized phase, patients continued treatment with lithium or valproic acid and were randomized to receive either ziprasidone (administered twice daily totaling 20 mg or 2 mg, up to QID) or placebo. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. The primary endpoint in this study was time to recurrence of a mood episode (manic, mixed or depressed episode) requiring intervention, which was defined as any of the following: discontinuation due to a mood episode, clinical intervention for a mood episode (e.g., initiation of medication or hospitalization), or Mania Rating Scale score of no less than 4 hours. In the other study, the higher dose was 14.3 mg. The results of the intramuscular ziprasidone trials follow: Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at intervals of no more than 10 hours. In the other study, the higher dose was 8 mg, which could be given up to 4 times in the 24 hours of the study, at intervals of no less than 4 hours.

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The results of the intramuscular ziprasidone trials follow:

- In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.
- In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.
Information for patients taking GEODON or their caregivers

This summary contains important information about GEODON. It is not meant to take the place of your doctor's instructions. Read this information carefully before you take GEODON. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about GEODON.

What Is GEODON?

GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder. GEODON can also be used as maintenance treatment of bipolar disorder when added to lithium or valproate.

Who Should Take GEODON?

Only your doctor can know if GEODON is right for you. GEODON may be prescribed for you if you have schizophrenia or bipolar disorder. Symptoms of schizophrenia may include:

- hearing voices, seeing things, or sensing things that are not there (hallucinations)
- beliefs that are not true (delusions)
- unusual suspiciousness (paranoia)
- becoming withdrawn from family and friends

Symptoms of manic or mixed episodes of bipolar disorder may include:

- extremely high or irritable mood
- increased energy, activity, and restlessness
- racing thoughts or talking very fast
- easily distracted
- little need for sleep

If you show a response to GEODON, your symptoms may improve. If you continue to take GEODON there is less chance of your symptoms returning. Do not stop taking the capsules even when you feel better without first discussing it with your doctor.

It is also important to remember that GEODON capsules should be taken with food.

What is the most important safety information I should know about GEODON?

GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with a diagnosis of psychosis related to dementia treated with antipsychotics are at an increased risk of death when compared to patients who are treated with placebo (a sugar pill).

GEODON is an effective drug to treat the symptoms of schizophrenia and the manic or mixed episodes of bipolar disorder. However, one potential side effect is that it may change the way the electrical current in your heart works more than some other drugs. The change is small and it is not known whether this will be harmful, but some other drugs that cause this kind of change have in rare cases caused dangerous heart rhythm abnormalities. Because of this, GEODON should be used only after your doctor has considered this risk for GEODON against the risks and benefits of other medications available for treating schizophrenia or bipolar manic and mixed episodes.

Your risk of dangerous changes in heart rhythm can be increased if you are taking certain other medicines and if you already have certain abnormal heart conditions. Therefore, it is important to tell your doctor about any other medicines that you take, including non-prescription medicines, supplements, and herbal medicines. You must also tell your doctor about any heart problems you have or have had.

Who should NOT take GEODON?

Elderly patients with a diagnosis of psychosis related to dementia. GEODON is not approved for the treatment of these patients.

Anything that can increase the chance of a heart rhythm abnormality should be avoided. Therefore, do not take GEODON if:

- You have certain heart diseases, for example, long QT syndrome, a recent heart attack, severe heart failure, or certain irregularities of heart rhythm (discuss the specifics with your doctor)
- You are currently taking medications that should not be taken in combination with ziprasidone, for example, dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.

What To Tell Your Doctor Before You Start GEODON

Only your doctor can decide if GEODON is right for you. Before you start GEODON, be sure to tell your doctor if you:

- have had any problem with the way your heart beats or any heart related illness or disease
- have had any problem with fainting or dizziness
- are taking or have recently taken any prescription medicines
- are taking any over-the-counter medicines you can buy without a prescription, including natural/herbal remedies
- have had any problems with your liver
- are pregnant, might be pregnant, or plan to get pregnant
- are breast feeding
- are allergic to any medicines
- have ever had an allergic reaction to ziprasidone or any of the other ingredients of GEODON capsules. Ask your doctor or pharmacist for a list of these ingredients
- have low levels of potassium or magnesium in your blood

Your doctor may want you to get additional laboratory tests to see if GEODON is an appropriate treatment for you.

GEODON And Other Medicines

There are some medications that may be unsafe to use when taking GEODON, and there are some medicines that can affect how well GEODON works. While you are on GEODON, check with your doctor before starting any new prescription or over-the-counter medications, including natural/herbal remedies.

How To Take GEODON

- Take GEODON only as directed by your doctor.
- Swallow the capsules whole.
- Take GEODON capsules with food.
- It is best to take GEODON at the same time each day.
- GEODON may take a few weeks to work. It is important to be patient.
- Do not change your dose or stop taking your medicine without your doctor’s approval.
- Remember to keep taking your capsules, even when you feel better.

Possible Side Effects

Because these problems could mean you’re having a heart rhythm abnormality, contact your doctor IMMEDIATELY if you:

- Faint or lose consciousness
- Feel a change in the way that your heart beats (palpitations)
Common side effects of GEODON include the following and should also be discussed with your doctor if they occur:

- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Restlessness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea
- Rash
- Increased cough / runny nose

If you develop any side effects that concern you, talk with your doctor. It is particularly important to tell your doctor if you have diarrhea, vomiting, or another illness that can cause you to lose fluids. Your doctor may want to check your blood to make sure that you have the right amount of important salts after such illnesses.

For a list of all side effects that have been reported, ask your doctor or pharmacist for the GEODON Professional Package Insert.

**What To Do For An Overdose**

In case of an overdose, call your doctor or poison control center right away or go to the nearest emergency room.

**Other Important Safety Information**

A serious condition called neuroleptic malignant syndrome (NMS) can occur with all antipsychotic medications including GEODON. Signs of NMS include very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure. NMS is a rare but serious side effect that could be fatal. Therefore, tell your doctor if you experience any of these signs.

Delayed-onset drug reaction called drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with ziprasidone. Signs of DRESS may include rash, fever, and swollen lymph nodes. Other severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome may occur with ziprasidone. Signs of Stevens-Johnson syndrome may include rash with blisters which could include ulcers in mouth, skin shedding, fever and target-like spots in the skin. DRESS and other SCAR are sometimes fatal; therefore, tell your doctor immediately if you experience any of these signs.

Adverse reactions related to high blood sugar (hyperglycemia), sometimes serious, have been reported in patients treated with atypical antipsychotics.

There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these reactions. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Dizziness caused by a drop in your blood pressure may occur with GEODON, especially when you first start taking this medication or when the dose is increased. If this happens, be careful not to stand up too quickly, and talk to your doctor about the problem.

Before taking GEODON, tell your doctor if you are pregnant or plan on becoming pregnant. It is advised that you don’t breast feed an infant if you are taking GEODON.

Because GEODON can cause sleepiness, be careful when operating machinery or driving a motor vehicle.

Since medications of the same drug class as GEODON may interfere with the ability of the body to adjust to heat, it is best to avoid situations involving high temperature or humidity.

It is best to avoid consuming alcoholic beverages while taking GEODON.

Call your doctor immediately if you take more than the amount of GEODON prescribed by your doctor.

GEODON has not been shown to be safe or effective in the treatment of children and teenagers under the age of 18 years old.

**Keep GEODON and all medicines out of the reach of children.**

**How To Store GEODON**

Store GEODON capsules at room temperature (59°F to 86°F or 15°C to 30°C).

**For More Information About GEODON**

This sheet is only a summary. GEODON is a prescription medicine and only your doctor can decide if it is right for you. If you have any questions or want more information about GEODON, talk with your doctor or pharmacist. You can also visit [www.geodon.com](http://www.geodon.com).

This product's label may have been updated. For current full prescribing information, please visit [www.pfizer.com](http://www.pfizer.com)

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